REMARKS

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1 and 64 are amended to recite specific embodiments. In particular, the claims now recite that the organic complex and antigen are "associated by electrostatic interaction only," as taught at page 11, lines 23-25. These amendments are made without prejudice or disclaimer and Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application.

Upon entry of the amendments, claims 1, 44-45, 49-66, and 70-99 will remain pending. Claims 1, 44-45, 49-55, 63-66, 70-76 and 84-85 are under examination, while claims 56-62, 77-83 and 86-99 are withdrawn from consideration. These claims are retained as subject to rejoinder upon allowance of the elected subject matter.

II. Office Interview

Applicants thank the Examiners for the courtesies extended during the Office Interview on January 22, 2009. Applicants' statement of the substance of the interview is provided here, in accordance with MPEP § 713.04. As reflected in the Interview Summary, all prior art rejections were discussed. In particular, as discussed in more detail below, Applicants explained the cited references' failure to anticipate the claimed invention under §102, and also explained the inability of any combination of the cited references to render the invention obvious under §103. As reflected in the Interview Summary, Applicants also discussed the possibility of amending the claims along the lines of the amendments submitted herewith. Moreover, while the possibility of submitting further evidence of non-obviousness was mentioned, Applicants also noted that it would be improper to require such evidence where no prima facie case of obviousness had been established.

III. Novelty

A. Rejections over Simmonds

Claims 1, 44, 49-55, 64-66 and 70-76 85 stand rejected as allegedly anticipated by Simmonds A (WO 94/25602; §102(b)); Simmonds B (U.S. Patent 6,881,821; § 102(e)); or Simmonds C (U.S. Patent 7,198,892; §102(e)), in light of teachings by Sjolander (1998). As discussed during the Office Interview, the Simmonds references simply do not teach the claimed invention.

The pending claims are directed to "an immunogenic complex comprising a negatively charged organic complex and a positively charged antigen, which organic complex and antigen are associated by electrostatic interaction only," and wherein the charged antigen comprises one or more polypeptides from a specified region of HCV, and to compositions comprising such a complex. This subject matter is not taught or suggested by the Simmonds references (collectively, "Simmonds").

As explained previously and during the Office Interview, Simmonds A-C are directed to peptides that are described as being type-specific to HCV-4, HCV-5, and HCV-6. Thus, the focus of Simmonds A-C is the description of these peptides *per se*, not their formulation into novel immunogenic complexes, as claimed. The only portion of Simmonds with any relevance to the present invention appears to be the bald statement that the disclosed peptides "may optionally be ***attached*** to a particulate structure, such as liposomes or ISCOMS" (emphasis added). This teaching, however, does not anticipate the present invention, because it only suggests "attaching" the peptides to an ISCOM, not preparing an immunogenic complex where the organic complex and a positively charged antigen are associated by electrostatic interaction only, as recited in the instant claims.

Moreover, Simmonds does not inherently anticipate the claimed immunogenic complex, for at least two reasons:

First, Simmonds does not even inherently disclose the attachment of a ***positively*** charged antigen to a negatively charged ISCOM. Page 3 of the Office Action states that Simmonds teaches that "any antigen of HCV . . . is suitable for attaching to ISCOM or

liposome." Indeed, this finding supports Applicants' position, because it recognizes that there is no guidance in Simmonds to chose a positively charged antigen over a negatively charged or neutral antigen. Moreover, as explained previously, the peptides described in Example 3 of Simmonds are negatively charged, and so could not be associated with a negatively charged organic complex by electrostatic interaction only.

Second, Simmonds does not even inherently disclose preparing an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction only. As discussed during the Office Interview, at the time of the present invention, the art taught several different ways to attach antigens to ISCOMs, including by hydrophobic interaction and covalent attachment. For example, the Sjolander (1998) reference cited in the Office Action describes a hydrophobic interaction-based dialysis method that involves the incubation of components with detergent followed by removal of detergent to formation ISCOM. *See, e.g.,* Sjolander at pg. 326. For the described method to be effective, mixed micelles comprising saponin, cholesterol, phospholipid and protein are induced by addition of detergent. Removal of detergent by, *e.g.*, dialysis results in the formation of ISCOMs, provided that the protein has hydrophobic regions to participate in the formation of the mixed micelles, which are the required starting point for ISCOM formation. Figure 1 of Sjolander shows spikes of haemaglutinin incorporated into ISCOMs via their hydrophobic regions in accordance with this process.

Barr et al., *Adv. Drug. Deliv. Rev.* 32: 247-71 (1998) (submitted previously), focuses on hydrophobic interactions and mentions covalent chemical coupling as an alternative for non-amphipathic molecules. *See, e.g.,* Barr at pg. 254. Other references submitted herewith further support Applicants' position:

Cox & Coulter, *BioDrugs* 12: 439-53 (1999) (copy attached), provides a table (Table I) of "[m]echanisms whereby immunogen and adjuvant can associate." ISCOMs are listed as examples of hydrophobic interactions, covalent bonding and chelation ("iscomatrix"), and are ***not*** listed as an example of electrostatic interaction. *See, e.g.,* Cox & Coulter (1999) at pg. 441.

Cox & Coulter, *Vaccine* 15: 248-56 (1997) (copy attached), describe immunogenic ISCOMs as "ISCOMs into which protein or other immunogenic molecules have been incorporated," and teach that "[i]t is important to incorporate immunogen into ISCOM for an effective CTL response." In contrast, they describe aluminum salt gels as being "bound by electrostatic interaction" to immunogens. *See, e.g.,*Cox & Coulter (1997) at pg. 250-51.

Cox & Coulter, "Advances in Adjuvant Technology and Application," in ANIMAL PARASITE CONTROL UTILIZING BIOTECHNOLOGY (Yong, ed.) (CRC Press, 1992) (copy attached), teaches that peptides can be incorporated into ISCOMS "either directly or by chemical coupling to a carrier protein . . . after incorporation of [the] protein," and teaches modifications of peptides to enhance hydrophobic interactions to facilitate incorporation into ISCOMS. *See, e.g.,*Cox & Coulter (1997) at pg. 60.

None of these references, and none of the references cited in the Office Action, teaches an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction only. Inherent anticipation is not met by mere possibilities or probabilities. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002); *Scaltech, Inc. v. Retec/Tetra, LLC.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999). Because Simmonds' antigens could be "attached" to ISCOMs in a manner that does ***not*** involve electrostatic association, the record does not support the Examiner's inherent anticipation theory. To the contrary, the assumption that the attachment of antigen and organic complex necessarily or inherently would be by electrostatic interaction is ***incorrect***, because the state of the art included other methods of attachment. Indeed, as reflected in the foregoing references, prior to the present invention it was believed that a successful antigen-ISCOM association required a hydrophobic region on the antigen or covalent/chemical coupling between the antigen and ISCOM. It is only Applicant who determined that a positively charged antigen could be associated with an ISCOM by electrostatic interactions only, thus permitting the preparation of an immunogenic complex by a relatively simple, yet surprisingly stable, process.

Page 3 of the Office Action alleges that because Simmons teaches a composition comprising "an HCV antigen, and an organic complex of ISCOM . . . this is sufficient enough

to meet the limitation cited in the rejected claims." As discussed during the Office Interview, this finding is simply ***not true***, as it overlooks the recitations in the instant claims of, for example, (i) a positively charged antigen selected from a recited list and (ii) an electrostatic association between the antigen and ISCOM.

For at least these reasons, the §102 rejections based on Simmonds A-C are improper and should be withdrawn.

B. Rejections over Garcon

Claims 1, 44, 49, 50, 51, 54, 55, 64, 70-72 and 75-76 stand rejected as allegedly anticipated by Garcon (WO 96/33739). As discussed during the Office Interview, Garcon does not teach the claimed invention.

As explained previously and during the Office Interview, Garcon is broadly directed to vaccine compositions comprising an antigen, saponin, a sterol and, in some embodiments, MPL. Most of the disclosure and examples of Garcon relates to its "preferred compositions" which comprise liposomes. Page 2 states that the invention includes "compositions where the sterol/immunologically active saponin fraction forms an ISCOM structure." Again, Applicants emphasize that that is the ***only*** teaching Applicants could find in Garcon that relates to ISCOMs. At pages 4-5 of the Office Action, the Examiner appears to assume that any formulation with QS21 and sterol is an ISCOM formulation, but that is ***not true***. Garcon expressly teaches liposome preparations comprising QS21 and cholesterol. *See, e.g.*, Garcon at pg. 6-7.

Page 5 of the Office Action cites a passage from page 2 of Garcon, stating that the antigen can be "contained within the vesicle membrane or contained outside the vesicle membrane." This passage again relates to liposomes (the vesicle membrane), and in no way suggests an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction.

Like the Simmonds references, Garcon fails to teach or suggest either (i) the selection of a positively charged antigen or (ii) the preparation of an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction only, as recited in the

instant claims. Page 5 of the Office Action asserts that "the attachment of a HCV antigen to negatively charged ISCOM is inherently an interaction between the negatively charged ISCOM and positively charged HCV antigen. Otherwise, if the HCV antigen does not have [an] opposite charge, the attachment would not occur." Again, this statement is ***not true***.

As shown above, the art recognized that antigens could be associated with ISCOMs via methods that do not depend on electrostatic interaction, such as by hydrophobic interactions and covalent bonding. Indeed, as Applicants pointed out previously and discussed during the Office Interview, the patents cited in Garcon as describing methodologies that can be used in making its vaccines relate to encapsulation with liposomes (U.S. Patent 4,235,877), and conjugation to macromolecules (U.S. Patent 4,372,945 and U.S. Patent 4,474,757). Thus, the Examiner's assumption that the mention of ISCOMs inherently teaches an electrostatic interaction between the ISCOM and antigen is ***incorrect*** and contrary to the state of the art. Moreover, the Examiner's assumption that the mention of ISCOMs inherently teaches the selection of a positively charged antigen that could be electrostatically associated with the ISCOM is likewise ***incorrect*** and contrary to the state of the art.

The §102 rejection also completely ignores the recitations regarding the identity of the HCV antigen. As discussed during the Office Interview, Garcon does not teach or suggest the any of the specific HCV antigens within the scope of the instant claims.

For at least these reasons, the §102 rejections based on Garcon are improper and should be withdrawn.

IV. Non-Obviousness

Claims 1, 44, 49-55, 63-66, 70-76 and 84-85 stand rejected under §103 as allegedly obvious over Simmons A-C in combination with Cerny (1995). Claims 1, 44-45, 49-55, 63-66, 70-76 and 84-85 are newly rejected under §103 as allegedly obvious over Garcon in combination with Cerny (1995). Applicants respectfully traverse these rejections.

The inability of the Simmonds references and/or Garcon to teach or suggest the claimed invention is shown above. While Cerny is cited for teaching HCV T-cell epitopes,

combining Simmonds or Garcon with Cerny does not teach or suggest the claimed immunogenic complexes. In particular, combining Simmonds/Garcon with Cerny still leaves the skilled artisan with no guidance to (i) select a positively charged antigen and (ii) form "an immunogenic complex comprising a negatively charged organic complex and a positively charged antigen," wherein the "organic complex and antigen are associated by electrostatic interaction only."

Page 6 of the Office Action states that 8 of 9 epitopes in Table II of Cerny are positively charged. Applicants do not understand how the Examiner arrived at this conclusion. At neutral (e.g., physiological) pH, amino acids D and E are negatively charged and amino acids K and R are positively charged. Amino acid H is positively charged at pH 6.0, but is generally treated as neutral at pH 7.0. All other amino acids are uncharged. Thus, peptides 1 and 6 of Cerny Table II are positively charged, peptides 2 and 9 are negatively charged, and the others are neutral. So Cerny, like the other cited references, provides no teaching or suggestion to select a positively charged antigen as claimed.

Even under the Examiner's interpretation, the cited combination of references does not make the invention obvious, because the record still fails to provide any reasoning or motivation that would have led the skilled artisan to select a positively charged antigen from the antigens described in Cerny. Again, the Office Action appears to back into the invention, assuming that the mention of ISCOMs in Simmonds and Garcon would have implied the formation of an electrostatic association, which would have required the selection of a positively charged antigen to associate with the negatively charged ISCOM, but the foregoing disproves that theory.

Applicants have demonstrated that the mention of ISCOMs would not have been understood to require the formation of an electrostatic association between the negatively charged ISCOMs and a positively charged antigen because, for example, the art taught that ISCOMs could be associated with antigens via hydrophobic attractions or covalent attachment. Thus, the mention of ISCOMs would not have provided any motivation to select a positively charged antigen.

Moreover, even if a positively charged antigen were selected, the record still fails to provide any reasoning or motivation that would have led the skilled artisan to form an immunogenic complex where the organic complex and antigen are associated by electrostatic interaction only. To the contrary, the record shows that the conventional approach in the art would have been to use hydrophobic attractions or covalent attachment.

Thus, the cited combination of references wholly fails to suggest the claimed immunogenic complexes.

When the cited references are read in the context of the state of the art without improper hindsight, it is apparent that they do not teach or suggest the claimed invention. Thus, the §103 rejections are improper and should be withdrawn.

IV. Concluding Remarks

Applicants believe that this application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned attorney by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extensions under 37 C.F.R. §1.136 and authorize payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date February 26, 2009

By Courtenay C. Brinckerhoff

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4094
Facsimile: (202) 672-5399

Courtenay C. Brinckerhoff
Attorney for Applicant
Registration No. 37,288